



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 401/04, A61K 31/435	A1	(11) International Publication Number: WO 99/01450 (43) International Publication Date: 14 January 1999 (14.01.99)
(21) International Application Number: PCT/US98/13433 (22) International Filing Date: 1 July 1998 (01.07.98) (30) Priority Data: 08/886,766 2 July 1997 (02.07.97) US (71) Applicant: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US). (72) Inventors: SCHUMACHER, Doris, P.; 11 Lockhaven Court, Bedminster, NJ 07921 (US). LEE, Junning; 503 Meyersville Road, Gillette, NJ 07933 (US). ROGERS, Lawrence, R.; Apartment 303, 510 Millburn Avenue, Short Hills, NJ 07078 (US). ECKHART, Charles, G.; 9 Village Park Court, Scotch Plains, NJ 07076 (US). SAWANT, Naneshwar, S.; 17 Churchill Road, Edison, NJ 08820 (US). MITCHELL, Michael, B.; 40 Melbourne Way, Basking Ridge, NJ 07920 (US). (74) Agents: HOFFMAN, Thomas, D. et al.; Schering-Plough Corporation, Patent Dept., K-6-1 1990, 2000 Galloping Hill Road, Kenilworth, NJ 07033-0530 (US).		(81) Designated States: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CZ, EE, GE, GW, HR, HU, ID, IL, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: POLYMORPHS OF 8-CHLORO-6, 11-DIHYDRO-11- (4-PIPERIDYLIDENE) -5H-BENZO[5,6] CYCLO-HEPTA[1,2-b]PYRIDINE		
(57) Abstract <p>Crystalline polymorphs of 8-chloro-6, 11-dihydro-11-(4-piperidylidene) -5H-benzo[5,6] cyclohepta[1,2-b]pyridine represented by formula (I), pharmaceutical compositions containing such polymorphs, and methods of using such polymorphs to treat allergic reactions in mammals such as man are disclosed.</p> <div data-bbox="893 1155 1299 1470"><p>(I)</p></div>		

BEST AVAILABLE COPY

FOR THE PURPOSES OF INFORMATION ONLY

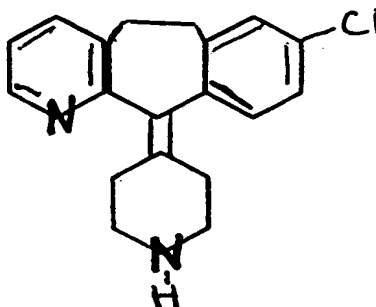
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

POLYMORPHS OF 8-CHLORO-6, 11-DIHYDRO-11- (4-PIPERIDYLIDENE) -5H-BENZO[5,6] CYCLO-
HEPTA[1,2-b]PYRIDINE

Background of the Invention

This invention relates to crystalline polymorphs of 8-chloro-6,11-dihydro-11-(4-piperidylidene)-5H-benzo[5,6]cyclohepta[1,2-b]pyridine (hereinafter "descarbonylethoxyloratadine") represented by the formula



pharmaceutical compositions containing such polymorphs, and methods of using such polymorphs to treat allergic reactions in mammals.

U.S. Patent No. 4,659,716 discloses descarbonylethoxyloratadine which possesses antihistaminic properties with substantially no sedative properties. This U.S. Patent also discloses methods of making descarbonylethoxyloratadine and using it to treat allergic reactions in mammals.

To prepare pharmaceutical compositions containing descarbonylethoxyloratadine for administration to mammals in accordance with exacting health registration requirements of the U.S. and international health registration authorities, e.g. the FDA's Good Manufacturing Practices ("GMP") requirements, there is a need to produce descarbonylethoxyloratadine in as pure a form as possible, especially a form having constant physical properties.

Summary of the Invention

We have discovered that descarbonylethoxyloratadine can exist in the form of two distinct crystalline polymorphs, each having distinctly different physical properties.

Accordingly, this invention provides crystalline polymorph form 1 descarbonylethoxyloratadine essentially free of polymorph form 2 and characterized by the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") at approximately:

<u>d spacing</u> (± 0.04)	<u>RI</u>
9.04	Weak
6.42	Weak
5.67	Weak
5.02	Weak
3.58	Weak

This invention also provides crystalline polymorph form 1 descarbonylethoxyloratadine essentially free of polymorph form 2 and characterized by the following x-ray powder diffraction pattern essentially free of polymorph form 2 and having characteristic peaks expressed in terms of "d" spacings and relative intensities ("RI")(s=strong, m=medium, w=weak, v=very and d=diffuse) at approximately:

<u>d spacing</u>	<u>RI</u>	
9.04	W	
7.24	M	
7.11	VWD	
6.69	M	
6.42	W	
6.02	W	
5.84	VW	
5.67	W	
5.02	W	
4.73	M	
4.54	W	
4.48	W	
4.40	M	
4.29	WD	

4.25	W	
4.18	VS	
3.72	W	
3.68	W	
3.63	W	
3.58	W	
3.52	M	
3.45	W	
3.37	S	
3.23	W	
3.19	M	
3.14	VWD	
3.10	VWD	
3.04	M	
2.99	VWD	
2.93	VWD	
2.87	VWD	
2.84	W	
2.79	VWD	
2.73	VWD	
2.70	VWD	
2.65	W	
2.57	VWD	
2.56	VWD	
2.55	VWD	
2.51	VWD	
2.48	VWD	
2.47	VWD	
2.44	VWD	
2.42	WD	
2.37	VWD	
2.34	WD	
2.32	WD	
2.29	VWD	
2.27	W	

This invention further provides crystalline polymorph form 2 descarbonylethoxyloratadine substantially free of polymorph form 1 and characterized by the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") approximately:

d spacing (± 0.04)RI

8.34

Weak

6.87

Medium

6.20

Medium

4.90

Medium

This invention also provides crystalline polymorph form 2 descarbonylethoxyloratadine substantially free of polymorph form 1 and characterized by the following x-ray powder diffraction having characteristic peaks expressed in terms of "d" spacing and relative intensities ("RI") s=strong, m=medium, w=weak, v=very and d=diffuse) at approximately:

d spacing	RI
8.34	W
7.21	W
6.87	M
6.75	M
6.20	M
6.04	M
5.91	VW
4.90	M
4.71	M
4.64	M
4.50	WD
4.39	VS
4.34	S
4.19	VWD
4.08	W
3.95	S
3.84	M
3.66	S
3.52	W
3.46	W
3.45	WD
3.39	W
3.25	S
3.18	W
3.11	W
3.07	M
2.95	W
2.88	WD
2.81	WD
2.79	WD
2.72	VW
2.59	VW

	2.51	WD
	2.45	VWD
	2.40	VWD
	2.38	VWD
	2.32	VWD
	2.30	VWD

Brief Description of the Drawings

Figure 1 presents the infrared spectrum of crystalline polymorph form 1 descarbonylethoxyloratadine as a mull in mineral oil.

Figure 2 presents an infrared spectrum of crystalline polymorph form 2 descarbonylethoxyloratadine as a mull in mineral oil.

Detailed Description of the Invention

By the phrase "polymorph form 1 essentially free of polymorph form 2" as used herein means that descarbonylethoxyloratadine polymorph form 1 prepared in accordance with this invention contains less than about 1% of form 2 as measured by infrared spectral analysis on a FTIR spectrometer. The polymorph form 1 prepared in accordance with Examples 1 and 2 had no detectable amount of form 2 by FTIR spectrophotometry. By the phrase "polymorph form 2 substantially free of polymorph form 1" as used herein means that the descarbonylethoxyloratadine polymorph form 2 prepared in accordance with this invention contains less than about 15%, preferably less than about 10%, and more preferably less than about 5-8% of form 1 as measured by infrared spectral analysis on a FTIR spectrometer.

Descarboxyloratadine prepared as described in U.S. Patent No. 4,659,716 was isolated as the acetic acid salt (Example III) and as a mixture of polymorphs of the free base from hexane (see Examples V + VI).

We have discovered that descarbonylethoxyloratadine exists as a mixture of polymorphs. Such a mixture could lead to production of a descarbonylethoxyloratadine product which would exist as a variable mixture of variable composition (i.e., variable percent amounts of polymorphs) having variable physical properties, a situation unacceptable in view of stringent GMP requirements.

We have discovered specific solvents and experimental conditions which consistently produce two distinctly different crystalline polymorphs of descarbonylethoxyloratadine thereby allowing commercial production of a consistent pharmaceutical product having constant physical properties.

In the course of developing pure descarbonylethoxyloratadine crystalline polymorphs for a pharmaceutical composition prepared in compliance with exacting GMP regulations, we tried many solvent systems, most of which produced only mixtures of polymorphs. Surprisingly we discovered that certain alcoholic solvents, e.g., hexanol and methanol produced 100% polymorph form 1, but others, e.g., 3-methyl-1-butanol and cyclohexanol produced significant amounts of form 2. Chlorinated solvents, e.g., dichloromethane produced form 1 substantially free of form 2 but the compounds were discolored. Ether solvents such as dioxane produced form 1 substantially free of form 2 but other alkane ethers, e.g., diisopropyl ether produced form 1 with significant amounts of form 2 and di-n-butyl ether favored formation of form 2. Ketones such as methyl isobutyl ketone produced crystalline polymorph form 1 essentially free of form 2 but methyl butyl ketone produced a 8:1 ratio of form 1 to form 2. Use of methyl isobutyl ketone is preferred to produce crystalline polymorph form 1 essentially free of form 2.

Only ethyl acetate and di-n-butyl ether were found to produce crystalline polymorph form 2 substantially free of form 1. Use of di-n-butyl ether is preferred for producing crystalline form 2 substantially free of form 1.

The infrared spectrum of crystalline polymorph form 1 descarbonylethoxyloratadine taken on as a mull in mineral oil is characterized by the following three characteristic peaks(in reciprocal centimeters) not found in pure polymorph form 2 at approximately:

frequency (cm⁻¹)

3303

1290

803

780

A more complete infrared spectrum of crystalline polymorph form 1 descarbonylethoxyloratadine taken as a mull in mineral oil is characterized by the following characteristic peaks(in reciprocal centimeters) at approximately:

frequency (cm⁻¹)

3303
3052
3012
1636
1586
1566
1357
1331
1290
1273
1249
1231
1219
1201
1190
1177
1142
1119
1100
1086
1057
1029
1008
987
946
934
906
882
873
847
816
803
780
767
726
703
681
642
572

<u>frequency</u> <u>(cm⁻¹)</u>
549
530
520
498
490
449

The infrared spectrum of crystalline polymorph form 2 descarbonylethoxyloratadine taken as a mull in mineral oil is characterized by the following five characteristic peaks(in reciprocal centimeters) not found in the polymorph form 1 at approximately:

frequency (cm⁻¹)

3326

1153

1133

795

771

655

A more complete infrared spectrum of crystalline polymorph form 2 descarbonylethoxyloratadine taken as a mull in mineral oil is characterized by the following characteristic peaks(in reciprocal centimeters at approximately:

frequency (cm⁻¹)

	3326	
	3304	
	3052	
	3015	
	1635	
	1586	
	1569	

	<u>frequency</u> <u>(cm⁻¹)</u>	
	1558	
	1479	
	1456	
	1437	
	1420	
	1398	
	1383	
	1328	
	1301	
	1282	
	1265	
	1250	
	1199	
	1174	
	1153	
	1133	
	1118	
	1089	
	1010	
	977	
	951	
	915	
	887	
	868	
	846	
	816	
	795	
	781	
	771	
	730	
	707	
	688	
	655	
	623	
	570	
	550	
	528	
	515	
	493	
	467	
	447	

These infrared spectra were obtained on mulls in mineral oil measured a Mattson Galaxy 6021 FTIR spectrometer. The mineral oil mulls were prepared and placed between NaCl or KBr plates in accordance with the USP procedure <197M>. See also "Experiments in Techniques of OInfrared Spectroscopy", R.W. Hannah and J. S. Swinehart, Perkin-Elmer Corpation , September,1974, pps, 6-1 to 6-6. The spectral data was presented in absorbance from about 3370 to 3250 cm^{-1} . The area of the peaks at $3326 \pm 1 \text{ cm}^{-1}$ (form 2) and at $3303 \pm 1 \text{ cm}^{-1}$ (form 1) were integrated to obtain the ratio of form 2 to form 1.

The x-ray powder diffraction patterns were measured on a Philips APD3720 automated diffractometer system (model PW 1800). The radiation source was copper (K-alpha) and the long fine focus tube connected to a Philips XRG 3100 x-ray generator operated at 45 KV and 40 mA. The take-off angle was 6 degrees and a graphite monochromator as used. A scintillation detector was employed and data was acquired with a scan rate of 0.025 degrees per second, a step size of 0.010 and a step time of 40 seconds per degree.

The x-ray powder diffraction pattern distinctive for crystalline polymorph form 1 descarbonylethoxyloratadine having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") is provided hereinbelow:

<u>"d" spacing</u> (± 0.04)	<u>RI</u>
9.04	Weak
6.42	Weak
5.67	Weak
5.02	Weak
3.58	Weak

A more complete x-ray powder diffraction pattern for crystalline polymorph form 1 descarbonylethoxyloratadine having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") is provided hereinbelow:

d spacing	RI	
9.04	W	
7.24	M	
7.11	VWD	
6.69	M	
6.42	W	
6.02	W	
5.84	VW	
5.67	W	
5.02	W	
4.73	M	
4.54	W	
4.48	W	
4.40	M	
4.29	WD	
4.25	W	
4.18	VS	
3.72	W	
3.68	W	
3.63	W	
3.58	W	
3.52	M	
3.45	W	
3.37	S	
3.23	W	
3.19	M	
3.14	VWD	
3.10	VWD	
3.04	M	
2.99	VWD	
2.93	VWD	
2.87	VWD	
2.84	W	
2.79	VWD	
2.73	VWD	
2.70	VWD	
2.65	W	
2.57	VWD	
2.56	VWD	
2.55	VWD	
2.51	VWD	
2.48	VWD	
2.47	VWD	
2.44	VWD	
2.42	WD	
2.37	VWD	
2.34	WD	
2.32	WD	
2.29	VWD	
2.27	W	

The x-ray powder diffraction pattern distinctive for crystalline polymorph form 2 having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") is provided hereinbelow:

<u>d spacings</u> (± 0.04)	<u>RI</u>
8.34	Weak
6.87	Medium
6.30	Medium
4.90	Medium

A more complete x-ray powder diffraction pattern for polymorph form 2 descarbonylethoxyloratadine having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") is provided hereinbelow:

d spacing	RI
8.34	W
7.21	W
6.87	M
6.75	M
6.20	M
6.04	M
5.91	VW
4.90	M
4.71	M
4.64	M
4.50	WD
4.39	VS
4.34	S
4.19	VWD
4.08	W
3.95	S
3.84	M
3.66	S
3.52	W
3.46	W
3.45	WD

	3.39	W
	3.25	S
	3.18	W
	3.11	W
	3.07	M
	2.95	W
	2.88	WD
	2.81	WD
	2.79	WD
	2.72	VW
	2.59	VW
	2.51	WD
	2.45	VWD
	2.40	VWD
	2.38	VWD
	2.32	VWD
	2.30	VWD

Pharmaceutical Compositions

Pharmaceutical compositions of this invention may contain in addition to an anti-allergically effective amount of crystalline polymorph form 1 or form 2 descarboxylethoxyloratadine as the active ingredient, inert pharmaceutically acceptable carriers that may be solids or liquids. Solid form compositions include powders, tablets, dispersible granules, capsules, cachets, and suppositories. A solid carrier can be one or more substances which may also act as diluants, flavoring agents, solubilizers, lubricants, suspending agents, binders or tablet disintegration agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active compound. In the tablet the active compound is mixed with carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain from about 5 to about 20 percent of the active ingredient. Suitable solid carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methycelulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter and the like. The term "compositions" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in

which the active component (with or without other carriers) is surrounded by carrier, which is thus in association with it. Similarly, caches are included. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for topical administration. Liquid preparations can also be formulated in solution in aqueous polyethylene glycol solution. Aqueous solutions suitable for oral use can be prepared by adding the active component in water and adding suitable colorants, flavors, stabilizing, sweetening, solubilizing and thickening agents as desired. Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, i.e., natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose and other well-known suspending agents.

Topical formulation useful for nasal or ophthalmic administration are also contemplated. Topical formulation suitable for nasal administration may be solutions or suspensions. Ophthalmic formulations may be solutions, suspension or ointments. Ointments usually contain lipophilic carriers such as mineral oil and/or petrolatum. Solution for ophthalmic administration may contain sodium chloride, acid and/or base to adjust the pH as well as purified water and preservatives.

The anti-allergic effective amount of polymorph form 1 or form 2 descarboxylethoxyloratadine for topical administration varies from 0.1 to 5% by weight of the total pharmaceutical composition. The preferred amount varies from 0.5 to 2% by weight of the total pharmaceutical composition.

The anti-allergic effective amount of polymorph form 1 or form 2 descarbonylethoxyloratadine for oral administration varies from about 1 to 50 mg/day, preferably about 2.5 to 20 mg/day and more preferably about 5 to 10 mg/day in single or divided doses. The most preferred amount is 5.0 mg, once a day.

Of course the precise dosage and dosage regimen may be varied depending upon the requirements of the patients. (e.g., his or her sex, age) as well as the severity of the allergic condition being treated. Determination of the proper dosage and dosage regimen for a particular patient will be within the skill of the attending clinician.

The polymorph form 1 and form 2 descarbonylethoxyloratadine possess antihistaminic properties. These antihistaminic properties have been demonstrated in standard animal models, such as prevention of histamine - induced lethality in guinea pigs. Antihistaminic activity of form 1 and form 2 has also been demonstrated in a monkey model.

Example 1

Preparation of polymorph form 1 descarbonyl-ethoxyloratadine.

To a solution of 60.0 kg of potassium hydroxide flakes in 200 liters of industrial methylated spirits was added 50.0 kg of loratadine (available from Schering Corporation, Kenilworth, NJ, see also U.S. Patent No. 4,282,233). The so-formed mixture was heated under reflux for 3 hours and 150 liters of water were added. The so-formed mixture was distilled at atmospheric pressure until a temperature of the mixture reached 108°C. The mixture was cooled to 68°C and 150 liters of methyl isobutyl ketone (MIBK) were added and the mixture was agitated until all the solids were dissolved. The organic layer was separated and washed with water at 80°C until the separated aqueous layer had a pH of 9. Fifty (50) liters of MIBK

were then removed from the organic layer by distillation at atmospheric pressure and the so formed organic layer was cooled to around 0°C for 1 hour. The resulting crystalline product was separated by centrifugation, washed with 2 x 12 liters of room temperature MIBK and spun dry in a centrifuge at high speed. The so-formed product was dried at 60°C for 6 hours to give 29.05 kg of polymorph form 1 descarbonylethoxyloratadine as a white crystalline solid, mp 156.8-157.7. The structure of the title compound was confirmed by comparison of its IR and NMR with spectra of a reference standard.

Example 2.

Preparation of polymorph form 1 descarbonylethoxyloratadine

Loratadine(45 Kg, 117 moles) was refluxed in about 180 liters of ethanol containing potassium hydroxide (about 40.5 Kg, excess) for about 5 hours to complete the carbamate hydrolysis(see also Example VI of U.S. Patent No. 4,659,716). The warm reaction mixture was diluted with about 135 liters of water and distilled at atmospheric pressure until a reaction mixture temperature of 105-110°C was achieved. The reaction mixture was then cooled to 50-70°C, diluted with about 135 liters of methyl isobutyl ketone (MIBK), and the so-formed mixture was reheated to 80-90°C to redissolve solids. The aqueous layer was separated, and the MIBK layer was washed with additional portions of water until a pH of 6-9 was achieved in the aqueous layer.

The MIBK layer was then concentrated under atmospheric pressure and slowly cooled to -5 to 0°C as crude descarbonylethoxyloratadine crystallized. Crude descarbonylethoxyloratadine was filtered, washed with MIBK, and dried at about 60°C to produce about 33.5 Kg (92% of theory) of crude descarbonyl-ethoxyloratadine which may also be carried into the next step as a wet cake.

Crude descarbonylethoxyloratadine (33.6 Kg, 108 moles) was dissolved in about 135 liters of hot (85-95°C) MIBK, filtered, and about 50 liters of the MIBK was distilled from the mixture at atmospheric pressure.

The so-formed solution was then slowly cooled to 15-22°C, aged for about an hour, and the resulting crystalline slurry of descarbonylethoxy-loratadine was filtered, washed with MIBK, and dried at about 80°C to produce 31 Kg (92% yield) of polymorph form 1 descarbonylethoxy-loratadine as a white crystalline solid. This white crystalline solid contained 100% of form I, with no detectable amount of form 2 by FTIR spectrophotometry.

Crystalline polymorph form 1 was micronized using a fluid energy mill and packaged in double polyethylene bags in a fiber drum closed with a metal ring.

Example 3

Alternative preparations of polymorph form 1 descarbonylethoxyloratadine

A. To a 50 mL Erlenmeyer flask was added 3.3 g of descarbonylethoxyloratadine (prepared in accordance with Example VI of U.S. Patent No. 4,659,716) and methanol (3.5 ml). The so-formed mixture was heated until complete dissolution was obtained. The so-formed clear solution was allowed to cool slowly to room temperature and kept at room temperature for 4 hours. The resulting crystalline product was filtered, washed with hexane (10 ml) and dried in a vacuum oven at 40°C under nitrogen for 24 hours to provide 2.77 g of polymorph form 1 descarbonylethoxyloratadine as a white crystalline solid, (DSC 157.30).

B. To a 250 mL three neck round bottom flask equipped with an overhead agitator, thermocouple and nitrogen gas source was added 10 g of descarbonylethoxyloratadine (prepared as described in Example VI of USP 4,65,716) and 60 mL of MIBK. The so-formed mixture was heated to 105 °C and the temperature was maintained at 105 °C until complete dissolution was obtained. The so- formed solution was slowly cooled to room temperature to allow the crystalline product to precipitate out of solution. The so-formed mixture was cooled to 5 °C and the temperature was maintained at 5 °C for 1 hour. The solid was vacuum filtered and washed with 2 volumes of MIBK (chilled to 5 °C) . The solid was dried in

an oven at 50 °C until the loss on drying was 0.4% or less. 8.30 g of polymorph form 1 descarbonylethoxyloratadine (100% by FTIR spectrophotometry) was obtained as a white crystalline solid.

Example 4

Preparation of polymorph form 2 descarbonyl-ethoxyloratadine.

A solution of 366 g of descarbonylethoxyloratadine (prepared as described in Example VI of USP 4,65,716) in 3 liters of ethyl acetate was heated to reflux; 15 g. of Darco decolorizing charcoal and 25 g of Supercel filtering aid were added and the so-formed mixture was further refluxed for 10 minutes. The mixture was filtered while hot through a Supercel filter mat. The filtrate was concentrated at elevated temperature to 650 ml. The so-formed concentrated filtrate was rapidly cooled to 0°C. The resulting precipitate was filtered, washed with hexane and dried in an air-draft oven at 55-60°C to give 333.2 g of polymorph form 2 descarbonylethoxyloratadine as a white crystalline solid, having mp 154.0-155.5°C, and containing 100% form 2 by FTIR spectrophotometry.

Example 5

Alternative Preparation of polymorph form 2 descarbonyl-ethoxyloratadine.

To a first 250 mL three neck round bottom flask ("first flask") equipped with an overhead agitator, thermocouple and nitrogen gas source was added 10g of descarbonylethoxyloratadine (prepared as described in Example VI of USP 4,65,716) and 150 mL of di-n-butyl ether. The so-formed mixture was heated to 100 °C and held at this temperature until all solid material dissolved, and a clear solution was formed. To a second 250 mL three neck round bottom flask ("second flask") equipped identically as the first flask was added 50mL of di-n-butyl ether. The second flask was cooled to -50 °C. A cendula was connected to both flasks and the ends of the

cendula were placed below the surface of the solutions in both flasks. Nitrogen pressure was applied to the first flask sufficient to completely force the solution in first flask into the second flask. The temperature of the second flask was maintained at below -20 °C and the so-formed very turbid solution in the second flask was stirred for five minutes. The resulting precipitate was vacuum filtered. The solid was dried in a vacuum oven under a nitrogen atmosphere at room temperature. No heat was applied to prevent discoloration of the product. Seven grams (7 g) of polymorph form 2 descarbonylethoxyloratadine was obtained as a crystalline solid which contained 92% (\pm 5%) of form 2 by FTIR spectrophotometry.

Stability Testing for Crystalline Polymorph Form 1

Samples of crystalline polymorph form 1 prepared in accordance with this invention were subjected to stability testing at various temperatures (25, 30 and 40 °C) and relative humidities of 60%, 60% and 75%, respectively. Assay for form 1 and total related compounds were performed including physical appearance, X-ray diffraction, FTIR (identity), FTIR (polymorph ratio) and pH. No significant change (<1%) from initial sample % form 1 and related compounds was observed.

What is claimed is

(1) Crystalline polymorph form 1 descarbonylethoxyloratadine essentially free of polymorph form 2 and characterized by the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") at approximately:

<u>d spacing</u> (± 0.04)	<u>RI</u>
9.04	Weak
6.42	Weak
5.67	Weak
5.02	Weak
3.58	Weak

(2) Crystalline polymorph form 1 descarbonylethoxyloratadine essentially free of polymorph form 2 and characterized by the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") (s=strong, m=medium, w=weak, v=very and d=diffuse) at approximately:

d spacing	RI	
9.04	W	
7.24	M	
7.11	VWD	
6.69	M	
6.42	W	
6.02	W	
5.84	VW	
5.67	W	
5.02	W	
4.73	M	
4.54	W	
4.48	W	
4.40	M	
4.29	WD	
4.25	W	
4.18	VS	
3.72	W	

3.68	W	
3.63	W	
3.58	W	
3.52	M	
3.45	W	
3.37	S	
3.23	W	
3.19	M	
3.14	VWD	
3.10	VWD	
3.04	M	
2.99	VWD	
2.93	VWD	
2.87	VWD	
2.84	W	
2.79	VWD	
2.73	VWD	
2.70	VWD	
2.65	W	
2.57	VWD	
2.56	VWD	
2.55	VWD	
2.51	VWD	
2.48	VWD	
2.47	VWD	
2.44	VWD	
2.42	WD	
2.37	VWD	
2.34	WD	
2.32	WD	
2.29	VWD	
2.27	W	

(3) The crystalline polymorph form 1 descarbonylethoxyloratadine of claim 1 further characterized by an infrared spectrum generated on a mull of the polymorph form 1 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm⁻¹)

3303

1290

803

780

(4) The crystalline polymorph form 1 descarbonylethoxyloratadine of claim 1 further characterized by an infrared spectrum generated on a mull of the polymorph form 1 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm⁻¹)

3303
3052
3012
1636
1586
1566
1357
1331
1290
1273
1249
1231
1219
1201
1190
1177
1142
1119
1100
1086
1057
1029
1008
987
946
934
906
882
873
847
816
803
780
767

<u>frequency</u> <u>(cm⁻¹)</u>
726
703
681
642
572
549
530
520
498
490
449

(5) The crystalline polymorph form 1 descarboxy loratadine of claim 2 further characterized by an infrared spectrum generated on a mull of said polymorph form 1 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm⁻¹)

3303

1290

803

780

(6) The crystalline polymorph form 1 descarbonylethoxyloratadine of claim 2 which is further characterized by infrared spectrum generated on a mull of said polymorph form1 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm⁻¹)

3303
3052
3012
1636
1586
1566
1357
1331

<u>frequency</u> <u>(cm⁻¹)</u>
1290
1273
1249
1231
1219
1201
1190
1177
1142
1119
1100
1086
1057
1029
1008
987
946
934
906
882
873
847
816
803
780
767
726
703
681
642
572
549
530
520
498
490
449

(7) A pharmaceutical composition comprising an anti-allergic effective amount of the crystalline polymorph form 1 descarboxyl-ethoxyloratadine of claim 1 and a pharmaceutically acceptable carrier.

(8) Crystalline polymorph form 2 descarbonylethoxyloratadine substantially free of polymorph form 1 and characterized by the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacing and relative intensities("RI") at approximately:

<u>d spacing</u> (± 0.04)	<u>RI</u>
8.34	Weak
6.87	Medium
6.20	Medium
4.90	Medium

(9) Crystalline polymorph form 2 descarbonylethoxyloratadine substantially free of polymorph form 1 and characterized by the following x-ray powder diffraction pattern having characteristic peaks expressed in terms of "d" spacings and relative intensities ("RI")(s=strong, m=medium, w=weak, v=very and d=diffuse) at approximately:

d spacing	RI
8.34	W
7.21	W
6.87	M
6.75	M
6.20	M
6.04	M
5.91	VW
4.90	M
4.71	M
4.64	M
4.50	WD
4.39	VS
4.34	S
4.19	VWD
4.08	W
3.95	S
3.84	M
3.66	S
3.52	W
3.46	W
3.45	WD
3.39	W
3.25	S

	3.18	W
	3.11	W
	3.07	M
	2.95	W
	2.88	WD
	2.81	WD
	2.79	WD
	2.72	VW
	2.59	VW
	2.51	WD
	2.45	VWD
	2.40	VWD
	2.38	VWD
	2.32	VWD
	2.30	VWD

(10) The crystalline polymorph form 2 descarboxy loratadine of claim 8 further characterized by an infrared spectrum generated on a mull of said polymorph form 2 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm⁻¹)

3326

1153

1133

795

771

655

(11) The crystalline polymorph form 2 descarbonylethoxyloratadine of claim 8 further characterized by an infrared spectrum generated on a mull of said polymorph form 1 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency(cm⁻¹)

	3326	
	3304	
	3052	
	3015	
	1635	
	1586	
	1569	
	1558	
	1479	
	1456	
	1437	
	1420	
	1398	
	1383	
	1328	
	1301	
	1282	
	1265	
	1250	
	1199	
	1174	
	1153	
	1133	
	1118	
	1089	
	1010	
	977	
	951	
	915	
	887	
	868	
	846	
	816	
	795	
	781	
	771	
	730	
	707	
	688	
	655	
	623	
	570	
	550	
	528	

	frequency(cm^{-1})	
	515	
	493	
	467	
	447	

(12) The crystalline polymorph form 2 descarbonylethoxyloratadine of claim 9 further characterized by an infrared spectrum generated on a mull of said polymorph form 2 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm^{-1})

3326

1153

1133

795

771

655

(13) The crystalline polymorph form 2 descarboxy loratadine of claim 9 further characterized by an infrared spectrum generated on a mull of said polymorph form 2 in mineral oil showing the following characteristic peaks in reciprocal centimeters at approximately:

frequency (cm^{-1})

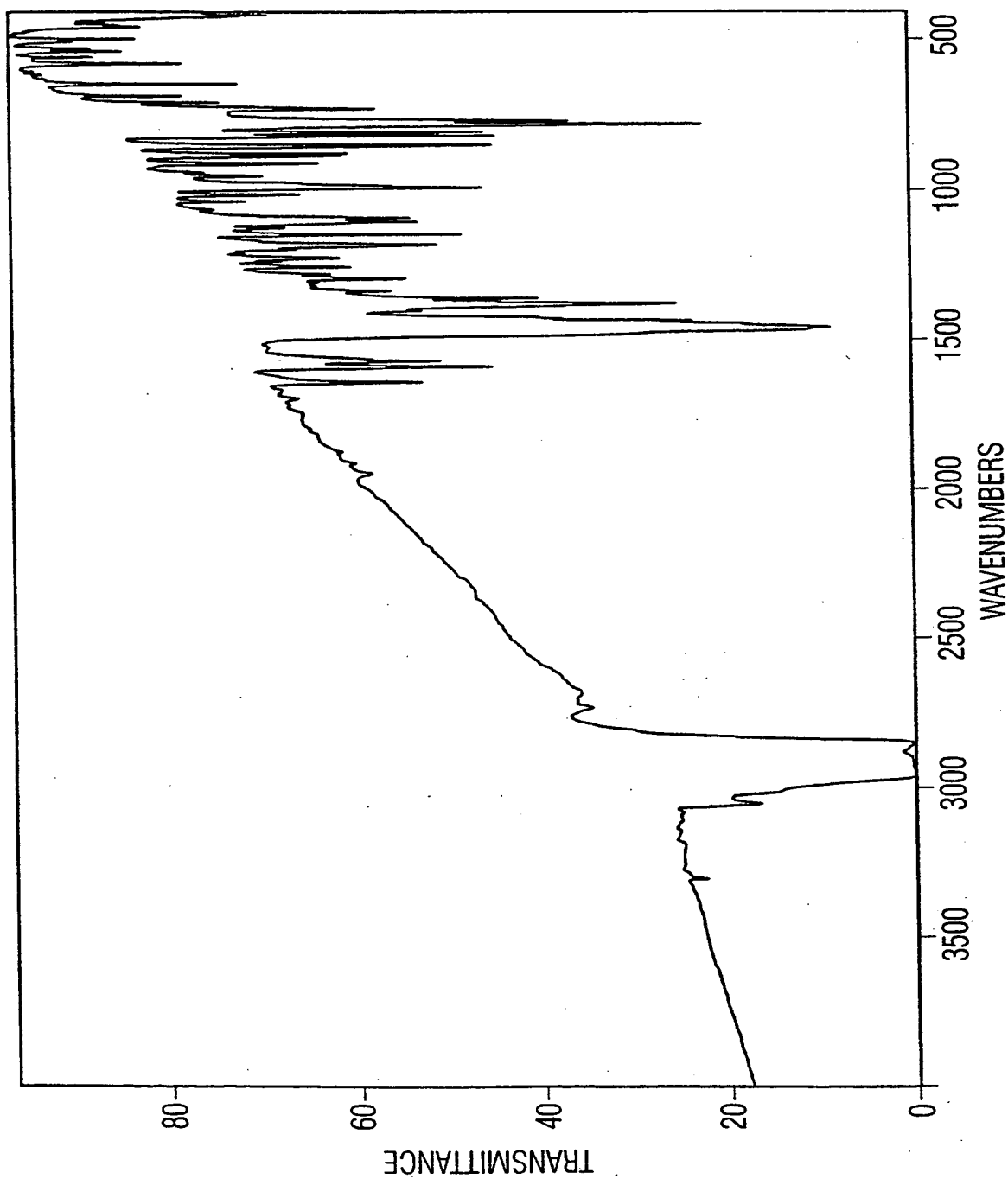
	3326	
	3304	
	3052	
	3015	
	1635	
	1586	

	<u>frequency</u> <u>(cm⁻¹)</u>	
	1569	
	1558	
	1479	
	1456	
	1437	
	1420	
	1398	
	1383	
	1328	
	1301	
	1282	
	1265	
	1250	
	1199	
	1174	
	1133	
	1118	
	1089	
	1010	
	977	
	951	
	915	
	887	
	868	
	846	
	816	
	795	
	781	
	771	
	730	
	707	
	688	
	655	
	623	
	570	
	550	
	528	
	515	
	493	
	467	
	447	

- (14) A pharmaceutical composition comprising an anti-allergic amount of the crystalline polymorph form 2 descarbonylethoxyloratadine of claim 8 and a pharmaceutically acceptable carrier.
- (15) A pharmaceutical composition comprising an anti-allergic amount of the crystalline polymorph form 2 descarbonylethoxyloratadine of claim 9 pharmaceutically acceptable carrier.
- (16) A pharmaceutical composition comprising an anti-allergic amount of the crystalline polymorph form 1 descarbonylethoxyloratadine of claim 2 and a pharmaceutically acceptable carrier.
- (17) A method of treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of the crystalline polymorph form 1 descarbonylethoxyloratadine of claim 1.
- (18) A method of treating allergic reactions in a mammal which comprises administering to said mammal an anti-allergic effective amount of the crystalline polymorph form 2 descarbonylethoxyloratadine of claim 8.

1/2

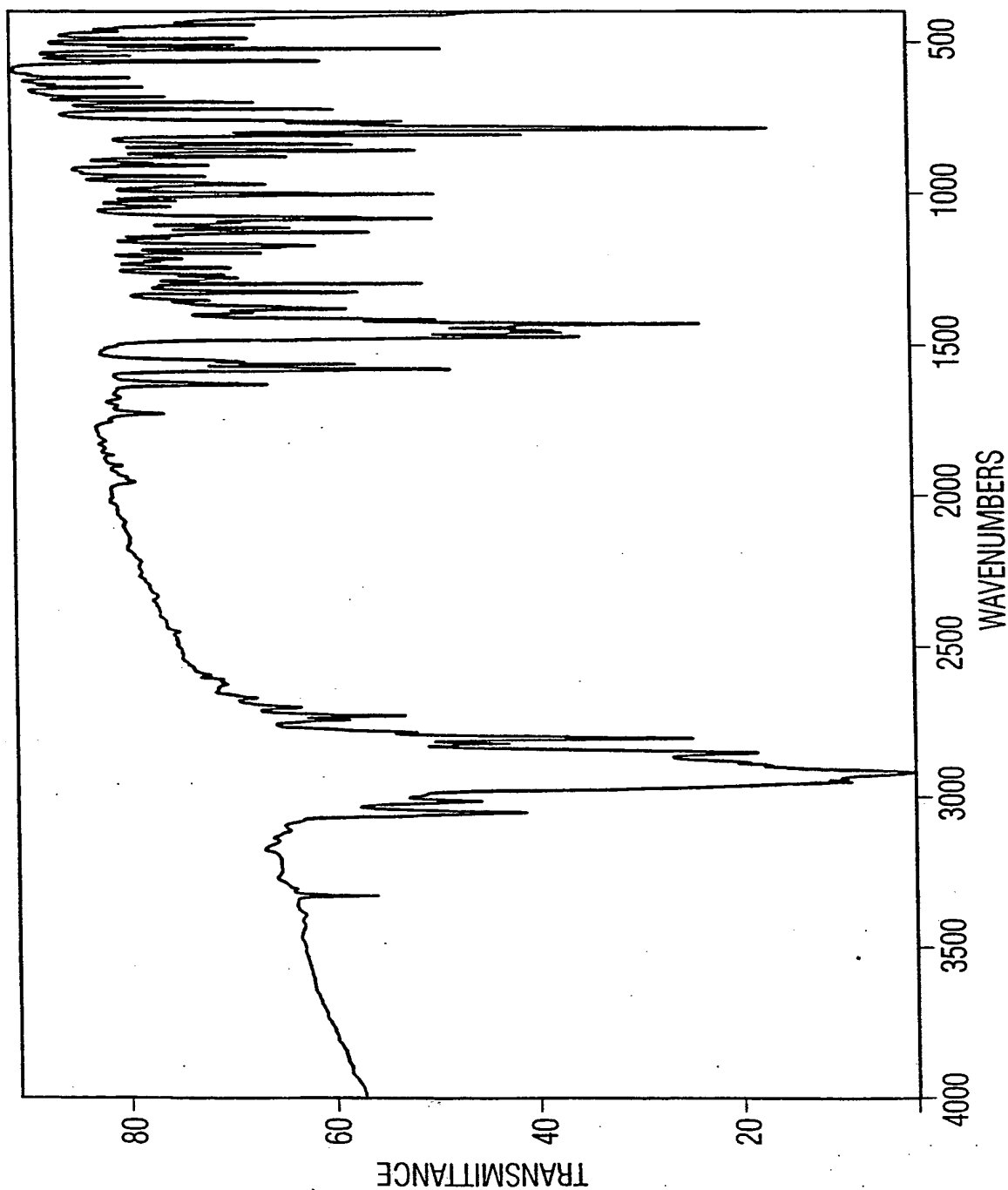
FIG. 1



SUBSTITUTE SHEET (RULE 26)

2/2

FIG. 2



SUBSTITUTE SHEET (RULE 26)

INTERNATIONAL SEARCH REPORT

Inter. Appl. No.

PCT/US 98/13433

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 C07D401/04 A61K31/435

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 152 897 A (SCHERING CORPORATION) 28 August 1985 cited in the application see claims -----	1-18

☐

Further documents are listed in the continuation of box C.

☒

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

Date of the actual completion of the international search

15 September 1998

Date of mailing of the international search report

23/09/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Henry, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 13433

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 18
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 18
is directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

International Application No

PCT/US 98/13433

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0152897 A	28-08-1985	AU 570306 B	10-03-1988
		AU 3993885 A	10-09-1985
		DK 469485 A,B,	14-10-1985
		FI 853675 A,B	25-09-1985
		JP 61501205 T	19-06-1986
		WO 8503707 A	29-08-1985
		US 4659716 A	21-04-1987

THIS PAGE BLANK (USPTO)

**This Page is Inserted by IFW Indexing and Scanning
Operations and is not part of the Official Record**

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☒ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☐ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** _____

IMAGES ARE BEST AVAILABLE COPY.

As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.

THIS PAGE BLANK (USPTO)